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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/065,163	09/23/2002	Thomas Alan Early	040849-0192	4876
22428	7590	06/15/2004	EXAMINER GAKH, YELENA G	
FOLEY AND LARDNER SUITE 500 3000 K STREET NW WASHINGTON, DC 20007			ART UNIT 1743	PAPER NUMBER

DATE MAILED: 06/15/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)	
10/065,163	EARLY ET AL.	
Examiner	Art Unit	
Yelena G. Gakh, Ph.D.	1743	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

**A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM
THE MAILING DATE OF THIS COMMUNICATION.**

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication. Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) Responsive to communication(s) filed on 29 April 2004.
- 2a) This action is **FINAL**. 2b) This action is non-final.
- 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) Claim(s) 4-12,14,17,18,20 and 23-25 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) Claim(s) _____ is/are allowed.
- 6) Claim(s) 4-12,14,17,18,20 and 23-25 is/are rejected.
- 7) Claim(s) _____ is/are objected to.
- 8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) The specification is objected to by the Examiner.
- 10) The drawing(s) filed on 23 September 2002 is/are: a) accepted or b) objected to by the Examiner. Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a). Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
 - a) All b) Some * c) None of:
 1. Certified copies of the priority documents have been received.
 2. Certified copies of the priority documents have been received in Application No. _____.
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) Notice of References Cited (PTO-892)
- 2) Notice of Draftsman's Patent Drawing Review (PTO-948)
- 3) Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____.
- 4) Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____.
- 5) Notice of Informal Patent Application (PTO-152)
- 6) Other: _____.

DETAILED ACTION

1. The amendment, remarks and Affidavit filed on 04/29/04 are acknowledged. Claims 4-12, 14, 17-18, 20 and 23-25 are pending in the application.

Response to Amendment

2. All rejections of the pending claims, as well as objection to the specification, remain as they were established in the previous Office action.

Specification

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. The specification is objected to as not containing a written description of the invention "in such full, clear, concise, and exact terms as to enable any person skilled in the art to ... to make and use the same and shall set forth the best mode". In particular, the specification discloses an example of applying the method of the instant application to a quantitative NMR analysis of a mixture of three relatively simple organic compounds: 2,4,6-trimethylphenol (mesitol), diethylphthalate and menthol, ¹H and ¹³C NMR spectra of which are depicted on Figures 1 and 2. However, on page 7, paragraph [0024] the reference is made to "20 mg of polymer" which "were dissolved in 0.5 ml of CDCl₃" for ¹H NMR and "about 250 mg of sample along with about 50 mg of Cr(acac)₃ were dissolved in 3.5 ml CDCl₃" for ¹³C NMR. It is not clear, what is this polymer, since no polymer was mentioned earlier in the Example, or what happens to this polymer further, since in "Results" on page 8 [0029] the specification returns back to the mixture of three small organic compounds? It is not clear, if a part of the specification, which relates to the polymer sample is missing, especially in the light of claims 12

and 20, which recite a polymer “comprising a soft segment BPA polycarbonate”, which has not been mentioned in the specification at all. Clarification of the specification is required.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1-10 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the case, when two or more components are not “distributed identically in the integral packets, i.e., the matrix A has two or more identical columns”, does not reasonably provide enablement for the latter very common case. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. As indicated by the inventors themselves, if two or more components are distributed evenly in the integral packets, “only the sum of concentrations of these two components can be calculated. Likewise, if the integral distribution of a component is a linear combination of the integral distribution of other components, then that component concentration will not be uniquely determined. In these cases, A and x need to be restated in terms of the new, reduced set of x” (Specification, page 4, paragraph [015]), which does not make sense in the case of a two-component system. Therefore, the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The specification is further enabling only for NMR spectra, for which signals are assigned at least to specific types of groups (e.g. methyl, methylene, methine, quaternary carbon, etc.) for each mixture component so that “identifying the number of nuclei that contribute to the integral data of said resonance packets” could be performed.

Regarding ^{13}C spectra the specification is enabling only for the spectra obtained under special conditions and for mixture components of similar structure, since relaxation times

determine the integral intensities of the signals, see e.g. Mareci et al. (1977), Yamazaki et al (1978), Alger et al. (1979), Laude et al. (1986).

7. Claim 12 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The specification does not provide enablement for the method for determining the relative concentration of two or more components in a sample containing a mixture of polymers, especially proteins. It is well known in the art, that assigning signals to at least specific groups in protein NMR spectra, which is a necessary step for performing the instant method, requires special techniques, such as multi-dimensional and/or relaxation experiments, including isotope enrichment of samples. The examiner is not aware of any reference providing assigning ¹H or ¹³C signals for protein molecules just from 1D NMR spectra, not mentioning the mixtures of proteins; no references could be found which provide information on the content of protein mixtures from 1D spectra. Moreover, no references indicate possibility of quantifying mixtures of complex compounds by applying linear regression analysis. Even spectra of mixtures of much simpler compounds require application of vigorous mathematical analysis, such as principal component analysis or neural network, see e.g. Wilson et al. (1989), Cheng et al. (1997, IDS), Amendolia et al. (1998), Alam et al. (2000). No examples of such quantitative analysis of proteins or synthetic polymers, including BPA polycarbonate, are represented in the specification.

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 11-12 and 17-18 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims recite “determining the relative concentration of two or more components in a sample”, wherein “said sample comprises a polymer”. It is not clear, which two or more components are meant here, if only one polymer (except for co-polymer) is present in the sample, especially if this polymer is a protein or a polypeptide.

Claim Rejections - 35 USC § 102

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

11. **Claims 4-5, 7-10, 14 and 24** are rejected under 35 U.S.C. 102(b) as being anticipated by Warren et al. (J. Pharm. Sci., 1976).

Warren teaches a “quantitative NMR analysis of a four-component mixture of phenylglycine derivatives”, comprising: obtaining ^1H NMR spectrum of the sample; identifying resonance packets from the spectrum, integrating said resonance packets; identifying the number of nuclei that contribute to the integral data of said resonance packets; and determining the relative concentration of each component in said sample based on the integral data and on the number of nuclei (the whole text, especially Table II).

12. **Claims 4-11, 14, 17-18, 23 and 25** are rejected under 35 U.S.C. 102(b) as being anticipated by Landucci et al. (Holzforschung, 1998).

Landucci teaches ^{13}C NMR quantitative spectroscopy for determining concentration of components in a mixture of polymers using resonance packets integrals and assigned signals with known contribution of particular nuclei to specific resonance packets and involving linear summation over corresponding spectral regions: “it is informative to compare the quantitative spectra along with integrals of carbon regions as shown in Figure 8. To obtain the integral values for the G-DHP it was assumed that the aromatic region contained 6.00 carbons plus a correction value (0.4) calculated for the presence of two unsaturated carbons (α and β) due to about one CA end group for every 6 C9 units (~17%). All of the other integrals in the spectrum are based upon these assumptions. It can be seen from the Figure that the sum of the aromatic and aliphatic regions total 10.0 carbons, which is expected considering one methoxy/C9 unit” (page 168, left column).

Claim Rejections - 35 USC § 103

13. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

14. The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

15. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

16. **Claims 15-16** are rejected under 35 U.S.C. 103(a) as being unpatentable over Landucci.

Although Landucci does not specifically disclose applying method to solid state NMR or implementing it in a quality assurance process, it would have been obvious for anyone of ordinary skill in the art to do so, because solid state NMR carries the same problems as solution NMR of polymer mixtures, i.e. the spectra have broaden and overlapping lines, for which the same principles that are used by Landucci can be easily implemented; quantified NMR is routinely applied for quality assurance processes. It would have been obvious to apply Landucci's method specifically to polycarbonate of claim 20, as it is another example of the polymer, which can be analyzed by this method

Response to Arguments

17. Applicant's arguments filed 04/29/04 have been fully considered but they are not persuasive.

Objection to the specification: amendment to the specification does not cure the deficiency of the originally filed specification. The only example disclosed in the specification starting with subparagraph [0023] refers to NMR analysis of a mixture of three relatively simple organic compounds. Subparagraph [0023] discloses the test sample of this mixture; Tables 1, 2 and 3 refer to this mixture; Figure 1 represents ^1H NMR spectrum of this mixture, etc. Excerpts regarding "20 mg of polymer" "dissolved in 0.5 ml of CDCl_3 " from [0024] do not have any apparent connection with the preceding or following subparagraphs. No real example for the polymer similar to the one for "test sample" is disclosed in the specification. The specification only states that "in a preferred embodiment the method is applied to a sample that comprises a mixture of polymers, where the polymer or mixture of polymers comprises a soft segment BPA polycarbonate". The only real example regarding BPA polycarbonate is provided by the Declaration. However, the Declaration is not a part of the disclosure and cannot be considered a confirmation of something that was not disclosed in the application.

Regarding the scope of enablement for claims 4-10 and 14-16. The present case is not the one, which may encompass non-operative embodiments. It is rather the case, when operative embodiments are limited to very specific conditions, clearly disclosed in the specification and emphasized in the Declaration (paragraph 8). All other embodiments are not enabled. Therefore, the citation of MPEP § 2164.08(b) is not relevant to the present application, and the method is enabled only for specific conditions indicated above.

Regarding the examiner's statement that 'the specification is further enabling only for NMR spectra, for which signals are assigned at least to specific types of groups (e.g. methyl, methylene, methine, quarternary carbon, etc.) for each mixture component so that "identifying the number of nuclei that contribute to the integral data of said resonance packets" could be performed': the Applicant did not explain, how the NMR spectra of e.g. polymer or protein mixtures (especially proton NMR) can be analyzed by the instant method, when there is uncertainty, as to which signals (CH_3 , CH_2 , CH) are overlapped in the spectrum. It is very

common in protein NMR to have signals of methylene groups of one protein overlapped with signals of methyne or methyl groups of another protein. If there is no preliminary knowledge on which groups have signals in a considered region (a “resonance packet”), how is it possible to identify “the number of nuclei that contribute to the integral data of said resonance packets”?

As for the references of Mareci, Yamazaki, Alger and Laude, they clearly indicate complexity of analysis of NMR spectra of protein mixtures. Polymers recited in claims 11, 17 and 25 can be proteins, as disclosed in the specification. By citing the references the examiner indicates that there is no way for anyone of ordinary skill in the art to find relative concentrations of proteins in protein mixtures by the method of the instant application, contrary to what is claimed.

The method of the instant application is applied to a particular case of differentiating between the polymer and one of the starting materials, which obviously have at least partially similar structure. There is no example for determining relative concentrations of polymers, and especially proteins, even from ^{13}C , not mentioning ^1H NMR spectra.

The method obviously works for ^{13}C spectrum of a mixture of BPA and PCP. However, this embodiment is not disclosed in the specification the way it is disclosed in the Declaration, and therefore is not enabled by the specification the way it is written. The method is not demonstrated to be operable for any mixture of non-analogous polymers or proteins, contrary to what is stated in the specification.

Claim rejection under 112, second paragraph. If components related to polymers recited in the claims are building blocks of a polymer or co-polymer, this term should be recited in the claims to clear the terminology of the claims.

Rejection over the prior art: obtaining NMR spectrum inherently comprises using internal standard, which usually is a deuterated solvent. While the instant method does not comprise comparing integrals using internal standard, internal standard is used for lock and calibration of NMR spectrum. Therefore, the amendment does not overcome the prior art of Warren.

The arguments regarding Landucci are not clear to the examiner. The arguments comprise a set of negative statements as to what Landucci allegedly did not do. The examiner cannot agree with such arguments. As far as the examiner understands, Landucci discloses exactly all the steps of the instant method: identification of resonance packets from the spectrum,

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integrating them, identifying the number of nuclei contributing to the packets and determining the relative concentration: "the aromatic region contained 6.00 carbons plus a correction value (0.4) calculated for the presence of two unsaturated carbons (α and β) due to about one CA end group for every 6 C9 units (~17%). All of the other integrals in the spectrum are based upon these assumptions. It can be seen from the Figure that the sum of the aromatic and aliphatic regions total 10.0 carbons, which is expected considering one methoxy/C9 unit" (page 168, left column)".

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Yelena G. Gakh, Ph.D. whose telephone number is (571) 272-1257. The examiner can normally be reached on 9:30 am - 6:00 pm.

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If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jill A. Warden can be reached on (571) 272-1267. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Yelena G. Gakh
6/11/04

A handwritten signature in black ink, appearing to read "Yelena Gakh".